PAIN® xxx (2013) xxx–xxx

PAIN®

www.elsevier.com/locate/pain

One night of total sleep deprivation promotes a state of generalized hyperalgesia: A surrogate pain model to study the relationship of insomnia and pain

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 1 January 2013
Received in revised form 3 April 2013
Accepted 19 April 2013
Available online xxxx

Keywords:
Sleep deprivation
Hyperalgesia
Quantitative sensory testing
Descending pain control
Fibromyalgia syndrome
Central sensitization

ABSTRACT

Sleep disturbances are highly prevalent in chronic pain patients. Understanding their relationship has become an important research topic since poor sleep and pain are assumed to closely interact. To date, human experimental studies exploring the impact of sleep disruption/deprivation on pain perception have yielded conflicting results. This inconsistency may be due to the large heterogeneity of study populations and study protocols previously used. In addition, none of the previous studies investigated the entire spectrum of nociceptive modalities. To address these shortcomings, a standardized comprehensive quantitative sensory protocol was used in order to compare the somatosensory profile of 14 healthy subjects (6 female, 8 male, 23.5 ± 4.1 year; mean ± SD) after a night of total sleep deprivation (TSD) and a night of habitual sleep in a cross-over design. One night of TSD significantly increased the level of sleepiness ($P < 0.001$) and resulted in higher scores of the State Anxiety Inventory ($P < 0.01$). In addition to previously reported hyperalgesia to heat ($P < 0.05$) and blunt pressure ($P < 0.05$), study participants developed hyperalgesia to cold ($P < 0.01$) and increased mechanical pain sensitivity to pinprick stimuli ($P < 0.05$) but no changes in temporal summation. Paradoxical heat sensations or dynamic mechanical allodynia were absent. TSD selectively modulated nociception, since detection thresholds of non-nociceptive modalities remained unchanged. Our findings show that a single night of TSD is able to induce generalized hyperalgesia and to increase State Anxiety scores. In the future, TSD may serve as a translational pain model to elucidate the pathomechanisms underlying the hyperalgesic effect of sleep disturbances.

1. Introduction

Chronic pain and co-morbid insomnia are recognized worldwide as serious health problems that severely impact patients' quality of life and productivity. Sleep disturbances are acknowledged among patients with nociceptive pain [1,46,85,90], neuropathic pain [59,106] and mixed pain conditions such as cancer [18,20,27,32] or low back pain [2,9,68,95]. In fibromyalgia syndrome (FMS), disturbed sleep is one of the key symptoms [47,54,58,71,80,82,83,91]. The high prevalence of insomnia in pain patients has prompted scientific interest in the interaction of sleep and pain, leading to the model of a vicious cycle between sleep disturbances and pain. Clinical observations, however, clearly challenge this hypothesis and rather point to a complex, non-linear relationship [28,60,62,87,89].

The impact of disturbed sleep on pain has been recently investigated in a number of human experimental studies that either explored effects on spontaneous pain, evoked pain, or both (for review see [57]). Though numerous studies suggest that spontaneous pain develops with quantitative accumulation of a sleep deficit [38–40], sleep fragmentation has been claimed to be the even more critical factor than sleep deficit *per se* [86]. Studies addressing the effects of disturbed sleep on evoked pain are largely conflicting. The majority of these focused on evaluation of pain sensitivity to blunt pressure and used a wide variety of study designs, including total sleep deprivation (TSD) of one [26,56,78] or several nights [40], sleep fragmentation [86], sleep restriction [38,39,81,86,92]

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0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2013.04.046

or selective sleep deprivation [5,61,71,72,75,78,81]. Some studies combined different sleep protocols to evaluate differential effects [78,81,86]. One night of TSD either decreased mechanical pain tolerance thresholds [78] or failed to reveal a significant effect [26,86]. Similarly, slow-wave sleep deprivation (SW-SD) was shown either to trigger pressure hyperalgesia [71,72,61], facilitate recovery from it [78], or proved ineffective [5,75]. Of the few sleep studies focusing on heat pain sensitivity, results are difficult to compare because of the divergent readout parameters previously used like the "heat pain threshold" [26,56,92], "heat pain *tolerance* threshold" [78], and the "withdrawal latency to a radiant heat stimulus" [81]. The small number of studies investigating effects of REM-SD either showed a lack of effect [72] or suggested an adverse effect on heat pain sensitivity [81].

While the inconsistency of previous sleep studies might be explained by study population heterogeneity and the technical methods used (see [57]), an important drawback of past efforts relates to the fact that none investigated the effects of disrupted/deprived sleep on the entire range of somatosensory modalities.

We aimed to address the previous shortcomings by applying a comprehensive, highly standardized and validated quantitative sensory testing protocol [33,84] in order to study the effects of sleep deprivation on *evoked pain*. Because a differential role of sleep stages on nociceptive processing has not been proven yet (see above), we elected to use one night of TSD as a model. A cross-over design was chosen to compare somatosensory profiles of young, healthy students after both TSD and a night of undisturbed sleep. Apart from effects on nociceptive and non-nociceptive modalities, spontaneous bodily complaints, mood changes and the level of sleepiness were assessed.

2. Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethical Committee of the Medical Faculty of Mannheim. All participants signed informed consent prior to study enrolment.

Fourteen healthy students with a mean age of 23.5 ± 4.1 years (8 male, 6 female; mean ± SD) were included in our study. According to their medical history and a physical and neurological examination, somatic or psychiatric diseases were excluded. Specifically, none of the volunteers had a history of a primary pain or headache disorder or any serious pain-associated physical trauma. None of the participants took analgesics except for minor and transient health problems such as flu-like symptoms. All volunteers were non-smokers.

All subjects were screened using the Beck Depression Inventory (BDI) [12] and the State and Trait Anxiety Inventory (STAI) [88]. Both BDI scores (cut-off: <11) and State Anxiety Scores (cut-off male students: 40.4 ± 8.5 (mean ± SD); cut-off female students: 41.7 ± 8.8 (mean ± SD)) were within normal limits and did not indicate depression or anxiety. Sleep history and scores of the Pittsburgh Sleep Quality Index [19,22] (2.2 ± 1.1; mean ± SD, range 0–4) indicated absence of sleep disturbances in study participants. Regarding caffeine consumption, 6 of them were habitually abstinent, the remainder ($n = 8$) drunk a maximum of 3 cups of coffee daily. Only females with a regular menstrual cycle were included. Since experiments exclusively took place during the transition time of the menstrual to follicular phase (see Table 1), females using contraceptives ($n = 4$) were investigated during their "pill pause." In 4 of 6 female subjects, the experiments were performed at exactly the same day of their menstrual cycle. In 2 females, for technical reasons, the second experiment had to be postponed for 1 and 4 days, respectively. Demographic data are shown in Table 1.

2.1. Study design

Subjects were asked to start filling in their sleep diaries 1 week before the index night. At 3 three days before the experiment, participants carried an Actiwatch Device (Philips Respironics®, Amsterdam) around the wrist. This piezoelectric device provides continuous motion data using a battery-operated microprocessor. The accompanying Respironics Actiwatch Software (Respironics Actiware Version 5.59.0015) allows translation of data into periods of "activity" and periods of "rest" and subsequent analysis of sleep parameters like "total sleep time." We chose an epoch length of 30 seconds for data sampling and a sensitivity threshold of 40 counts per epoch to define periods of activity. Ten minutes without signs of activity were set as cut-off to determine the beginning of the sleep phase.

According to our instruction, study participants remained abstinent from caffeine or caffeinated beverages 3 days before the experiment. A cross-over design in which all subjects were randomly assigned to either start with TSD or "habitual sleep" (HS) was used. In females, the interval between 2 index nights was adjusted to the menstrual cycle. In males, the interval between 2 index nights was 23 ± 9 days (mean ± SD). The night of HS was spent at home, monitored by Actiwatch Respironics. The night of TSD took place at the Institute where a medical student was advised to chat, play games, and go for short walks with the volunteer to keep him/her continuously active. By contrasting the test environment at the Institute with familiar surroundings at home, maximal sleep deprivation effects were elicited.

2.2. Index morning

All participants ate a standard breakfast (white bread, butter, honey, fruit tea or herbal infusion). In order to assess possible effects of sleep deprivation on spontaneous bodily discomfort or pain, all participants were asked about their well-being at the beginning of the day and spontaneous answers or complaints were noticed. After a drug screening test (Drug-Screen, nal vonminden GmbH, Germany), subjects had to fill in the State Inventory of the STAI and to indicate their subjective sleepiness by a Visual Analogue Scale (range 0–100). The quantitative sensory testing (QST) procedure always started at the same time at 9 am.

2.3. Quantitative sensory testing

For QST measures, quantitative sensory testing procedures implemented by the German Research Network on Neuropathic Pain (DFNS), were used to test the dorsum of both hands (see [84] for detailed description). Procedures lasted 60 minutes (30 minutes for each hand). Since changes in testing order can influence thresholds and ratings [36], which would increase data variance, testing was done in the following fixed order: CDT (cold detection threshold), WDT (warm detection threshold), TSL (thermal sensory limen), CPT (cold pressure threshold), HPT (heat pain threshold), MDT (mechanical detection threshold), MPT (mechanical pain threshold), MPS (mechanical pain sensitivity) including procedures to evaluate dynamic mechanical allodynia (DMA), WUR (wind-up ratio), VDT (vibration threshold) and PPT (pressure pain threshold).

In short, thermal detection and pain thresholds were assessed by using the TSA II NeuroSensoryAnalyzer (MEDOC, Israel) with a thermode surface of 9 cm^2. Thermal ramps of increasing/decreasing temperature (1°C/s) started from a baseline temperature of 32°C (low cut-off: 0°C; high cut-off: 50°C) and were performed 3 times. Volunteers had to press the button of a PC mouse connected to the device as soon as they felt the sensation specified in the instructions. Thresholds were determined by calculating the

Please cite this article in press as: Schuh-Hofer S et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: A surrogate pain model to study the relationship of insomnia and pain. PAIN® (2013), http://dx.doi.org/10.1016/j.pain.2013.04.046